UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,999	10/28/2003	Ilia Davydov	GRT/4504-2	4116

23117 7590 07/09/2007

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
DESAI, ANAND U	
ART UNIT	**PAPER NUMBER**
1656	
MAIL DATE	**DELIVERY MODE**
07/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,999	DAVYDOV ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8,10,15,17,35-47 and 57-66* is/are pending in the application.

4a) Of the above claim(s) *5-8,10,15,35-47 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3, 4, 17, 57-63, 65, and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to Amendment filed on April 10, 2007. Claims 1, 2, 12, 16, and 55 have been cancelled previously. Claims 5-8, 10, 15, 35-47, and 64 have been withdrawn previously.

2. Claims 3, 4, 17, 57-63, 65, and 66 are currently pending and are under examination.

Withdrawal of Rejections

3. The rejection of claims 3, 17, and 57 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Pending Rejections

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 3, 4, 17, 57-63, 65, and 66 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

6. The rejection was explained in the Office action mailed February 2, 2007.

Response to Remarks

7. Applicants' state the isolated conjugates have specific, substantial and credible utility. Applicants' state the invention provides a collection of ubiquitin conjugates of proteins that have

been linked to disease states. Applicants' state a person having ordinary skill in the art will readily recognize the utility of the invention in providing substrates, markers, and controls for studying the ubiquitylation and proteasomal degradation pathways as they relate to the diseases identifited in pages 6-22 of the specification. Applicants' state the claimed conjugates are biomarkers of clinically relevant ubiquitilation activity. The isolation of the conjugates from biological samples provides a material that is useful for quantifying ubiquitylation activity. The claimed conjugates are useful substrates that can be used in assays for quantifying the breakdown of ubiquitylated proteins mediated by the proteosome. Because of their usefulness in measuring these biological activities, the claimed materials are also useful for analyzing the effectiveness of drugs or other therapies against such activities. The claimed conjugates will have use as controls for assays and other studies. Applicants' state the utility of the claimed ubiquitin conjugates is readily apparent to one of ordinary skill in the art.

Applicant's arguments filed April 10, 2007 have been fully considered but they are not persuasive. The claims currently pending are drawn to an isolated conjugate comprising at least one ubiquitin or ubiquitin derivatized with another molecule, which is employed for purification or visualization; and a Markush of proteins including fragments and derivatives of proteins with at least 50 amino acids having at least 90% sequence identity to sequences within their corresponding proteins.

The specification describes the function for the specific proteins recited in the claims (see page 6, line 10 through page 22, line 23) for example, Aprataxin is a hydrolase that is mutated in ataxia-oculomotor apraxia syndrome. Synaptotagmin-like protein is believed to play a role in

regulation of vesicular trafficking. HMG17 is suggested to regulate chromatin structure and gene expression. PinX1 is a RNA processing protein, which inhibits telomerase activity.

However, the specification does not describe a specific and substantial utility for the conjugate of ubiquitin or ubiquitin derivative with the respective proteins or the composition comprising the conjugate. The specification states on page 23, line 1, that applicants have discovered that these proteins are targets for degradation via the N-end rule ubiquitylation pathway, and that controlling the rate of this degradation pathway provides an important mechanism for modulating the levels of these proteins and, thus, controlling disease states that are affected by the levels of these proteins. Furthermore, the disclosure does not describe a specific and substantial utility for fragments and derivatives of proteins with at least 50 amino acids having at least 90% sequence identity to sequences within their corresponding proteins. How would the fragments and derivatives that are not naturally present be used in the assays as controls as contemplated?

It is evident that regulating the interaction of the recited protein with ubiquitin would have an effect on the level of the protein, but it is unclear how once the protein already conjugated with ubiquitin can be used to inhibit the ubiquitylation process.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 3, 4, 17, 57-63, 65, and 66 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claims are rejected because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, and one skilled in the art clearly would not know how to use the claimed invention including the isolated conjugates drawn to ubiquitin or ubiquitin derivatizes conjugated with protein fragments and derivatives of proteins with at least 50 amino acids having at least 90% sequence identity to sequences within their corresponding proteins.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection

sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). References should be supplied if possible to support a prima facie case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

1) The nature of the invention: the instant claims are directed to an isolated conjugate comprising at least one ubiquitin or a ubiquitin derivatized with another molecule, which is employed for purification or visualization, and a protein, wherein said protein is selected from the group consisting of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, HSPC144, tau, Cullin 3, and CDC6, and fragments and derivatives thereof, wherein said fragments and derivatives thereof comprise polypeptides of at least 50 amino acids having at least 90% sequence identity to sequences within their corresponding proteins, and said conjugate is formed via N-end rule ubiquitylation.

2.) The breadth of the claims: the claims are extremely broad in that a very large number of constituents could be encompassed by fragments and derivatives of proteins selected from the group of proteins recited.

3) The predictability or unpredictability of the art: & 7.) The state of the prior art: there is unpredictability in the art with regard to the tertiary structure required for the interaction of substrate with the cognate E3 ubiquitin-protein ligase enzymes. Experiments have shown that optimal binding of substrate with E3 ubiquitin ligase may require a specific conformation (see Pickart, C. M. Annu. Rev. Biochem. 70: 503-533 (2001), particularly pp. 513-55, Ubiquitin-Protein Ligases (E3s); previously cited). Thus, there is no way to predict whether the fragments or derivatives will interact with E3 ubiquitin ligase.

Therefore, the unpredictability arises due to the differing conditions of starting materials, such as the genus of protein fragments and derivatives being claimed, and due to the different structures of the peptides.

4) The amount of direction or guidance presented: & 5) The presence or absence of working examples: the specification is devoid of any examples that conjugate fragments and derivatives of at least 50 amino acids having at least 90% sequence identity within the corresponding proteins. How would the fragments and derivatives that are not naturally present be used in the assays as controls as contemplated?

8.) Level of skill in the art: the level of skill in this art is high, at least that of a doctoral scientist with several years of experience in the art.

In consideration of the Wands factors, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Conclusion

10. No claims are allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on (517) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

July 2, 2007

AD
/Anand Desai/
Patent Examiner
Art Unit 1656

/Robert B. Mondesi/
Primary Patent Examiner
Art Unit 1652
July 3, 2007